Docket No.: 228-053 - 50198-079 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Trevor DOUGLAS et al. :

Serial No. 08/775,366 : Group Art Unit: 1648

Filed: January 3, 1997 : Examiner: J. Parkin

For: NANOSCALE PARTICLES SYNTHESIZED WITHIN AN ASSEMBLED VIRION

DECLARATION UNDER 37 CFR § 1.132

Honorable Commissioner of

Patents and Trademarks

Washington, D. C. 20231

Sir:

I, John E. Johnson, hereby declare and say as follows:

1. My curriculum vitae is attached.

2. I am familiar with the above-identified patent application directed to nanoscale particles and their synthesis within an assembled virion.

3. I understand, that while acknowledging novelty and unobviousness, the Patent Examiner has taken a position that the specification or the description of the invention "does not reasonably enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims."

4. I understand that the Examiner specifically notes that the breadth of the claims is exceedingly large and does not receive adequate written support, the disclosure only provides a limited number of working examples, and the disclosure fails to provide adequate guidance pertaining to the manipulation of the gating mechanism that allow the passage of organic and inorganic molecules into and out of the virion particle.

5. As will be apparent from my attached curriculum vitae, I have broad educational background and experience in virion technology. Accordingly, I have studied the disclosure of the

inventors Mark J. Young and Trevor Douglas with respect to whether I, as one of skill in this art, would find that the subject matter of the claims was adequately supported by the written description, and whether or not the description or disclosure would provide adequate guidance in the manipulation of gating mechanisms to allow the passage of organic and inorganic molecules into and out of the virion particles as set forth in the claims.

6. The invention in this patent application is directed to nanoscale particles, methods of making such particles and uses of the particles in various areas such as drug delivery and in other medical applications. As currently set forth, the patent application contains numbered claims 21-34. Claims 21-25 are directed to products and claims 26-34 are directed to process. The broadest product claim is claim 21 which reads as follows:

> 21. A plant virion-constrained nanoparticle comprising a shell of a plant virion coat protein surrounding a nanoparticle of non-viral origins selected from the group consisting organic, inorganic and organo-metallic materials.

The main product claim is limited to plant virions as noted by the claim language. On the other hand, main process claim 26 is directed to a method of producing nanoscale particles encased in a shell comprising one or more virion coat proteins. The claim is not limited to plant virions but covers any virion coat protein.

It is understood from the Examiner's writings in paragraph 4 of his Official Action of

February 3, 1999 that the process claims do not enable any person skilled in this art to make or use the invention in a manner which is commensurate in scope with the claims. Apparently, the Examiner considers that the supporting disclosure does not provide adequate guidance for the process claims because the cover any nanoscale particles encased within any virion coat protein. The Examiner refers to prior art as teaching that the mechanisms of viral assembly are complex and poorly understood and often require an orchestrated interaction between both viral and cellular proteins. The Examiner concludes that it is not readily manifest which viral coat proteins will function in the desired manner and that the limited number of species described in the written specification are not sufficient to support the breadth of the claims. In other words, the Examiner apparently considers that the number and type of working examples in the patent specification are not sufficient to support the broad terms in the claims, particularly with respect to more complex animal and human viruses which appear to be covered by the claims. Further, the Examiner holds that the disclosure fails to provide adequate guidance with respect to the gating mechanisms which allow the passage of organic and inorganic molecules into and out of the virion particle. The Examiner concludes that the prior art suggests that the assembly and formation of useful nanoparticles is replete with difficulties and that the specification fails to provide sufficient guidance concerning the consideration set forth in the Official Action.

7. In paragraph 5 of the Official Action, the Examiner makes basically the same rejections against the product claims as are made against the process claims, even though noting that the product claims are limited to coat proteins derived from a plant virus. It appears to be the

Examiner's position that each coat protein will have a unique amino acid sequence and unique structural and functional properties which would invite substantial experimentation before one could produce products covered by the claims based on the written description.

8. As noted above, I have studied the supporting description relied on by the inventors to support claims of the application. In that description, it appears clear to me that there is adequate experimental work in the patent specification as well as additional description, to enable one of skill in the art to practice the invention of the claims of the patent application. In the supporting specification, there is a general description of both the process and the products which would be well understood by one of skill in the art. Further, beginning at page 14, there is a definition of what is meant in the specification and claims by the term virions. General classes of virions are disclosed in the first paragraph on page 14. Protozoan, algal and fungal virions are listed at page 14, lines 10-12. Plant virions are listed on page 14, lines 13-24, virions of eukaroytic invertebrates are listed on page 14, line 25 to page 15, line 5, and virions of eukaroytic vertebrates are listed at page 15, line 6 to page 15, line 14. Virion constrained nanoparticles are defined on page 15, line 21 to page 16, line 4. Controlled gating is defined at page 15, lines 5-8. Thereafter, the invention is exemplified using the coat protein of the cowpea chlorotic mottle virus (CCMV).

At page 20, the virion constrained nanoparticles are described as being a variety of organic, inorganic and/or organo metallic materials ranging from single atoms or molecules to large conglomerates. A longlisting of suitable substances is then set forth at pages 20 and 21. At page 22, lines 20-24, it is pointed out that the invention may be used in conjunction with any virus coat

protein capable of forming a constrained environment. The claims of Young and Douglas make it clear that only if given a viral system that is (1) capable of assembling empty protein cages (devoid of viral nucleic acid) and (2) to which molecules have access to the interior cavity (via structural transitions such as gating or inherent openings in the protein shell) would the utility of using viral protein cages as constrained reactions vessels for the selective entrapment of molecules apply. The inventors are not claiming, or dependent on, the multitude of biochemical mechanisms displayed in different viral assembly systems to produce empty viral protein cages. However, once any virus system (animal, plant, insect, or bacterial virus) results in the assembly of empty viral protein cages, it is highly likely that it can serve the purpose as a constrained reaction vessel as described by the inventors. The ability of an empty viral protein cage to serve as a constrained reaction vessels as described by the inventors is clearly independent of the type of virus or the type of host cell that the virus infects. It is evident that many animal, plant, fungal, and bacterial viruses can be used as constrained reaction vessels as described by the inventors. This includes both in vitro and in vivo viral coat protein constrained environments. Various methods for carrying out controlled gating is set forth at page 23. The specification concludes with working examples directed to exemplification of the invention with the CCMV various.

9. There is also in the record of this patent application a Declaration of inventor Trevor Douglas. In the Declaration of Trevor Douglas, additional experimental work is presented showing the encapsulation of dextrine sulphate within CCMV and use of the invention with the tobacco

mosaic virus, TMV to provide the virus shell. This work of Dr. Douglas showed that the invention was easily applicable to the tobacco mosaic virus and did not require substantial experimentation.

10. There is also present in the record a Declaration of inventor Mark J. Young. The Declaration of Dr. Young provides the results of additional experiments which indicates that structures of more than 30 viruses have been determined to atomic resolution and that these structures reveal that the coat protein subunits of all virions are assembled and stabilized by non-covalent bond interactions such as H bonding, ionic interactions and hydrophobic interactions. Further, Dr. Young's Declaration states that the vast majority of icosahedral viruses have a coat protein sub-unit that utilizes a 8-stranded anti-parallel, _-barreled fold, commonly termed the "_ barrel jelly roll fold", which protein fold is dominant across all taxonomic classes of virus regardless of host. Dr. Young then lists various viruses CCMV, the human viruses Norwalk virus, Polio virus, Rhino virus, Parvo virus and Flockhouse virus which have this protein fold as the predominant structural feature. Dr. Young then presents evidence as having synthesized a paratungstate polymer using the virions protein cage of an animal Noralk virus (NWV) having icosheldral geometry and a constrained reaction vessel. Dr. Young also presents evidence of encapsulation of paratungstate within CCMV, and encapsulation of polyanetholesulfonic acid within CCMV, encapsulation of iron oxides within CCMV. Dr. Young then condudes that every system studied by the inventors has meet with success with only minor modifications being required in some cases.

11. Based on my review of the supporting disclosure for this patent application and the additional information presented in the Declarations of Dr. Douglas and Dr. Young, it appears clear

to me that the claims of the application are clearly adequately supported by the disclosure and the exemplary work set forth in the examples. The inventors have presented in this patent application a unique procedure using controlled gating mechanisms to provide a series of novel products of plant virion nanoparticles which have a shell of a plant virion coat protein surrounding a nanoparticle of non-viral origin. In my opinion, the disclosures in this patent application clearly teach one of skill in the art how to carry out the controlled gating process to produce the novel products of the invention. In my opinion, the scope of the claims is clearly enabled by the supporting description.

In the Official Action, the Examiner relies on certain prior art as raising questions about applicability of the invention to a wide variety of virion materials. In particular, the Examiner, on page 3 of the Official Action refers, to the publication by Douglas, *Biomimetic Mater. Chem.*, pages 91-114 (1996), as indicating that a number of limitations have preduded the advancement of synthesis of nanoscale particles into organized protein cages. This is the inventor Trevor Douglas's own publication and simply indicates on page 92 some difficulties to overcome problems with instability to particle aggregation and the like. However, this publication was made before the inventors completed their invention. There is evidence in the record from Dr. Douglas which clearly refutes these earlier writings. The Examiner therefore is relying on the publication by the inventor made before the invention was made. This publication is overcome by the inventors' representation in this patent application and Dr. Douglas's Declaration of record.

12. The Examiner also refers to a publication by Howk et al., Science 273:627-629, 1996, as disclosing several concerns regarding gating as a control element for nanoparticle loading. While

the Examiner points to concerns raised in this article, what is actually concluded in the Abstract is that gating has a critical influence on the ease of formation and stability of host guest complexes and that hosts equipped with gates can form very stable complexes with a variety of guests under readily achievable conditions. Therefore, this publication, relied on by the Examiner as suggesting concerns, actually shows that when used correctly, gating can be used as a control element under readily achievable conditions. Therefore, this article refutes the Examiner's suggestions.

13. At page 6 of the Official Action, the Examiner also refers to a publication by Dong et al., *Viriol*, 194:192-199, 1993, as suggesting that the prior art teaches that the mechanisms of viral assembly are complex and poorly understood. This publication was made in 1993, well prior to the filing of this patent application. This patent application presents a clear description of how controlled gating may be used. It is clear that Dong had no concept of the gating mechanism of this invention and should not be used as evidence to raise questions about the gating mechanism of this invention because Dong et al. is not concerned with the same processes. Once again, the claims of the inventors are not addressing the multitude of viral assembly mechanisms. They claim only that given a stable empty viral protein cage to which there is access to the virion's interior that it can be used as a constrained reaction vessel for selective material entrapment.

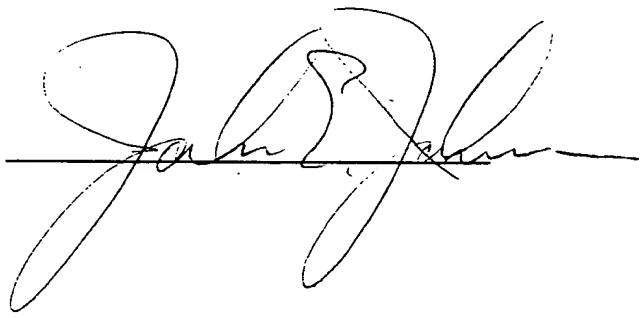
14. As a result of my study of the patent specification and claims of inventors Douglas and Young, the exemplary work and description set forth in that patent application, and the comments and the prior art relied on by the Examiner, it is my opinion that the claims of the patent application are fully supported by the description and the prior art raised by the Examiner is clearly

insufficient to support a theory that the claims are broader than the supporting description of the invention.

15. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Aug 19, 1999

Date



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Curriculum Vitae

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PERSONAL DATA

Born June 7, 1945; Oak Park, Illinois
Married Mary Lee Augustine, August 17, 1968
Son, Aaron Matthew, born 1973
Daughter, Melissa Lynn, born 1976

EDUCATION

Carthage College, Kenosha, Wisconsin
Bachelor of Arts, Chemistry
1963 - 1967

Iowa State University, Ames, Iowa,
Ph.D., Physical Chemistry
July 1967 - November 1972

APPOINTMENTS

The Scripps Research Institute, *Professor*, Department of Molecular Biology
July 1995 - Present
University of California, San Diego, *Adjunct Professor*, Department of Chemistry and Biochemistry, July 1998 - Present
The Scripps Research Institute, *Visiting Professor*, Department of Molecular Biology
January 1, 1993 - July 31, 1993
Purdue University, *Professor*, Department of Biological Sciences
July 1985 - June 1995
Associate Professor, Department of Biological Sciences
July 1981 - June 1985
Assistant Professor, Department of Biological Sciences
January 1978 - June 1981
Visiting Assistant Professor, Department of Biological Sciences
July 1975 - December 1977
Postdoctoral Research Associate, Department of Biological Sciences
September 1972 - July 1975
Institute Biologie Moleculaire et Cellulaire (CNRS),
Visiting Professor, Strasbourg, France, January 1, 1986 - July 31, 1986

SERVICE AND RECOGNITION

Editorial Board: **Structure with Folding & Design**, 1998 - Present
Editorial Board: **Journal of Molecular Recognition**, 1998 - Present
Editorial Board: **Virology**, 1998 - Present
Editorial Board: **Journal of General Virology**, 1998 - Present
Board of Scientific Counselors: **NIAMS (Arthritis, Musculoskeletal and Skin Diseases)**, 1996 - Present
Kaesberg Lecturer, **American Society of Virology Annual Meeting**, London, Ontario, 1996
International Commission on the **Taxonomy of Viruses**, 1994 - 1998
Board of Scientific Counselors: **National Cancer Institute**, Frederick, MD, 1994 - 1998
Associate Editor, **Biophysical Journal**, 1992 – 1998
Board of Governors for the **Consortium for Advanced Radiation Sources**, University of Chicago, 1991 - Present
Purdue Chapter Sigma Xi Faculty *Research Award Recipient*, 1989
Member, **National Institutes of Health Biophysical and Biochemical Study Section**, 1985 - 1989
Associate Editor, **Virology**, 1982 - 1995

PATENTS

Modified Plant Viruses as Vectors 11/96 European Patent No. 92 907 583.6
Modified Plant Viruses as Vectors 2/98 US Patent, approved/No.: pending.

FELLOWSHIPS

N.A.T.O. Travel Fellowship, September 1978
National Cancer Institute Postdoctoral Fellowship, Purdue University, West Lafayette, Indiana, 1974 -1976

PROFESSIONAL SOCIETIES

American Crystallographic Association
American Society for Virology
Protein Society
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PUBLICATIONS

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